ANEMIA IN TYPE 2 DIABETES MELLITUS

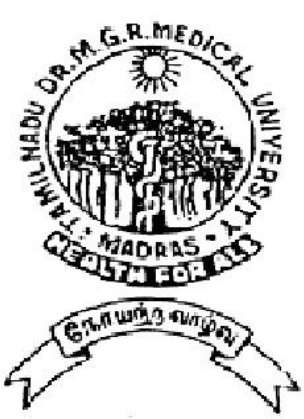
RISK FACTOR FOR THE PRESENCE AND SEVERITY OF MICRO VASCULAR COMPLICATION DIABETIC RETINOPATHY

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH - I (GENERAL MEDICINE)

APRIL 2011



THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"ANEMIA IN TYPE 2 DIABETES MELLITUS RISK FACTOR FOR THE PRESENCE AND SEVERITY OF MICRO VASCULAR COMPLICATION DIABETIC RETINOPATHY"** submitted by **Dr. P. SIVASUBRAMANIYA BARATHI** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D Degree Branch –I (General Medicine) is a bonafide research work carried out by him under my direct supervision & guidance.

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DECLARATION

I **Dr. P. SIVASUBRAMANIYA BARATHI** declare that, I carried out this work on, **"ANEMIA IN TYPE 2 DIABETES MELLITUS RISK FACTOR FOR THE PRESENCE AND SEVERITY OF MICRO VASCULAR COMPLICATION DIABETIC RETINOPATHY"** at the Department of Medicine, Govt. Rajaji Hospital during the period of October 2009 to September 2010. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any other University, Board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in General Medicine.

Place : Madurai **Dr. P. SIVASUBRAMANIYA BARATHI**

Date :

CONTENTS

ACKNOWLEDGEMENT

At the outset, I express my sincere thanks to **THE DEAN** for permitting me to use the facilities of Madurai Medical College and Government Rajaji Hospital to conduct this study.

I will remain in gratitude to my chief and head of the department of medicine **PROF.DR.MOSES K.DANIEL MD.,** not only for guiding me through the study, but also for being my mentor and source of inspiration during the period of my post graduate training. He has always guided me by example and valuable words of advice through the conduct of study. My sincere thanks to him.

Knowledge and kindness abounds to my beloved teachers **Dr.S.Vadivelmurugan MD., Dr.D.D.Venkatraman MD., Dr.V.T.Prem Kumar MD., Dr.M.Natarajan MD., Dr.Bagialakshmi MD., Dr.J.Sangumani MD** and **Dr.Dharmaraj MD. Retd Professors Dr. Ayyappan, M.D., Dr. Muthiah, M.D**., I owe them a lot and my sincere thanks to them.

I offer my special thanks to **Dr.Arthur Asirvatham, MD.,D.Diab**, head of the department of diabetology for his guidance and help and also thanks to **Dr. P. Thiyagarajan. M.S., D.O., HOD,** Ophthalmology for his valuable guidance.

I express my heartfelt thanks to my unit assistant professors **Dr.S. Murugesan, MD., Dr.R. Sundaram. MD.,** for their valuable support and guidance throughout my study.

I sincerely thank the staff of the Out patient Department for their cooperation & their support .

I profusely thank the Biochemistry Department for their cooperation and support.

I extend my thanks to my family and friends who have stood by me during my times of need. Their help and support have been invaluable to the study.

Finally, I thank all the patients, who form the most integral part of the work, were always kind and cooperative. I pray for their speedy recovery and place this study as a tribute to them.

Above all I thank the Lord Almighty for his kindness and benevolence.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action or both. It may be accompanied by the presence of progressive microvascular and macrovascular complications. The prevalence of type 2 diabetes is increasing all over the world. It has emerged as a major public health problem in India.

The WHO estimated that there were 31.7 million persons with diabetes in India in the year 2000 and this number is likely to rise by 71.4 million in 2030.[3]

The chronic complications of diabetes includes micro vascular complication and macrovascular complication.

The macrovascular complications includes the cardiovascular diseases, cerebrovascular diseases, peripheral vascular diseases. The microvascular complications includes diabetic retinopathy and diabetic nephropthy and diabetic neuropathy. Among the microvascular complication retinopathy is a dreadful sight

threatening one. Retinopathy is considered to be a leading cause of blindness in diabetic population.

Blindness is 25 times more common in diabetic patients than non diabetic. Diabetic retinopathy is ranked as the sixth common cause of blindness in India. While the type 2 diabetes mellitus patients may have retinopathy at the time of diagnosis. After two decades nearly 60% of the type 2 DM patients will have retinopathy. The scope of preventing, diagnosing and treating the devastating effects of retinopathy on vision is at present a major issue.[16]

The incidence of the diabetic retinopathy increases as the age advances. The relative risk is greater between the age of 30-60 years. The incidence of vision loss increases with increase in age, severity of retinopathy, duration of diabetes, presence of proteinuria and hyperglycemia.

Anemia, a common complication is more prevalent in persons with diabetes than in person without diabetes. Anemia can occurs in 25% of people with diabetes mellitus. Anemia may develop earlier and more severe in patients with diabetes than in patients with renal

impairment from other causes. The World Health Organisation WHO guidelines recommends investigation of anaemia where Hb is less than 12g /dl in women and less than 13g /dl in men.[16]

By using this definition nearly 1 among 4, that is 25% patients with diabetes have anemia. The cause of anemia in diabetic patient are diabetic nutritional deficiency, medications used for diabetics and related conditions and erythropoietin deficiency due to diabetic nephropathy.

Anemia along with diabetes may increase the likehood of developing retinopathy, cardiovascular and cerebro vascular events. People who have both anemia and diabetes are more likely to die earlier than those who have diabetes but not anemic. [25]

Anemia can lead to false low level of HbA1C which may result in under treatment of hyperglycemia which inturn will contribute to the progress of micro and macro vascular complications. [26]

Gender was considered as a significant influencing factor for the prevalence of anemia in population. Many of the studies have demonstrated the role of anemia, as an independent risk factor for diabetic retinopathy in patients with type 2 diabetes mellitus and the studies also have shown the influence of anemia on the severity of diabetic retinopathy in men and women.

REVIEW OF LITEATURE

Diabetes mellitus is now been established as one of the leading cause of morbidity and mortality throughout the world. Most of the ill effects on health can entirely be attributed to the long term complications of diabetes.

Chronic complications of Diabetes: [15]

The chronic complications of diabetes can be classified into microvascular complication and macrovascular complications traditionally.

Microvascular complication

Diabetic retinopathy

Diabetic nephropathy

Diabetic neuropathy

Macrovascular complication

Cardiovascular disease

Peripheral vascular disease

Cerebro vascular disease

Prevalence of chronic complications of Diabetes in an urban South Indian Population (Data from Chennai, urban population study (CUPS) and Chennai urban Rural Epidemiology study (CURES) by Mohan and Colleagues)[16]

Complication	Prevalence %
Diabetic retinopathy	17.6
Diabetic nephropathy	2.2
Diabetic neuropathy	17.5
Coronary artery disease	21.4
Peripheral vascular disease	6.3

Pathogenesis of Microvascular complications :[32]

The development of microvascular disease is related to both the duration as well as the severity of hyperglycemia. Hyperglycemia can lead to microvascular damage by several postulated mechanisms as detailed below. Although the precise mechanisms is not clear there are atleast four possible contributing mechanisms

1) accumulation of sorbitol and other polyols within endothelial cells.

2) Glucose induced protein kinase C up regulation with consequent prostaglandin production.

3) Glucose induced non enzymatic glycosylation of structural and functional proteins and

4) Glucose induced auto oxidative damage.

Polyol pathway

Activation of the aldose reductase pathway results in sorbitiol accumulation, decreased glutathione and production of diacyglycerol which in turn activates protein kinases and phospholipases. The net effect of activation of these biochemical intermediates is vasodilatation with resulting increased blood flow and increased vascular permeability.

The increased formation and accumulation of sorbitol in tissues is accompanied by a depletion of free myoinositol, loss of Na/K ATPase activity and increased consumption of the enzyme co-factors NADPH and NAD, leading to changes in cellular redox potential.

These metabolic derangements have been postulated to result in cellular dysfunction and ultimately the morphological lesions that are characteristic of diabetic retinopathy as well as nephropathy.

Increased Non-enzymatic glycosylation and formation of Advanced glycosylation End products

Glycosylated haemoglobin may decrease the ability of cells to release the oxygen. Alteration of structural cellular proteins may decrease the flexibility of red cells, making it more difficult to squeeze through capillaries, further decreasing their ability to provide oxygen to focal areas. The process of advanced glycation represents a complex series of reactions which occur when glucose and other reducing sugar react with proteins, lipids and nucleic acids. In diabetes, there occurs a sequence of biochemical reactions, many of which are still poorly defined, leading to the formation of a range of advanced glycation end products. (AGEs). AGEs bind to specific receptors in macrophages, endothelial cells and mesangial cells. Interaction of AGEs with their receptors in measangial cells leads to increased transforming growth factor (TGF-B) expression and extracellular matrix synthesis.

Growth factors :

Vascular endothelial growth factor (VEGF) and other growth factors have been identified in the retina. VEGF is up regulated in diabetic retinopathy and this has been found to correlate with the severity of the retinal changes, particularly neo vascularisation.

Protein Kinase C

Part of the adverse effects of hyperglycemia have been attributed to activation of protein kinase C (PKC), a family of serine threonine kinases that regulate diverse vascular functions, including contractility, blood flow, cellular proliferation and vascular permeability. Specific PKC inhibitors are now undergoing clinical trials in diabetic retinopathy and nephropathy.

DIABETIC RETINOPATHY

Diabetic retinopathy is the most common cause of blindness in diabetic population. Diabetic retinopathy is often asymptomatic in its most treatable stages ; hence early detection through regularly scheduled ocular examination is critical.

The prevalence of retinopathy at the time of diagnosis is much greater in type 2 (6.7 – 30.2%) as compared to type 1 (0-3%), as the former is more likely to remain undiagnosed for longer periods of time. Approximately 1 among 4 diabetes are unaware of their disease.

Prevalence of proliferative Diabetic retinopathy is more in long standing type 1 diabetes mellitus. However, in type 2 diabetes mellitus patients on insulin, risk is equally high (25%) possibly owing to chronic hyperglycemia. Most of the diabetic retinopathy patients seen in the clinics will be suffering from type 2, rather than type 1 diabetes simply because type 2 is seen more commonly in the population than type 1, though type 1 are more prone to develop retinopathy.

RISK FACTORS FOR THE DEVELOPMENT OF DIABETIC RETINOPATHY[32]

Poor control of Diabetes

Duration of diabetes

Hypertension

Nephropathy

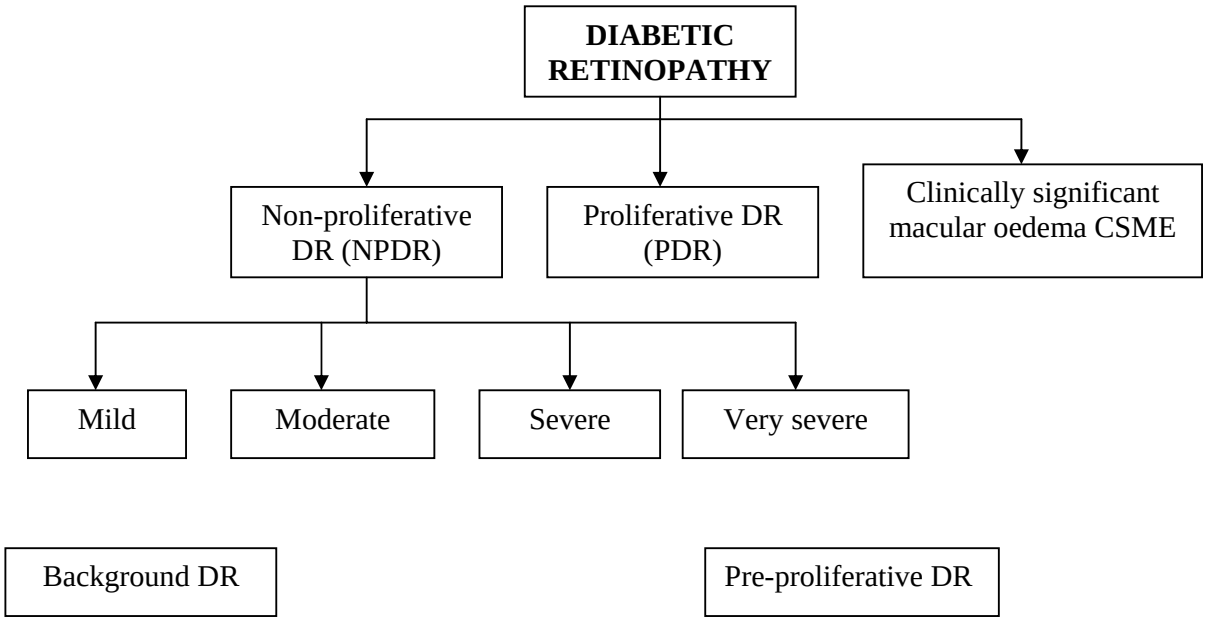
Obesity and hyperlipidemia

Smoking

Anemia

Pregnancy

Classification and Features



Mild and Moderate non- proliferative DR was previously known as Back ground DR. Severe and very severe Non-proliferative DR was known as the Pre-proliferative DR.

1. Non Proliferative Diabetic Retinopathy (NPDR)

Mild NPDR

- ❖ At least one microaneurysm – earliest clinically detectable lesion
- ❖ Retinal hemorrhages and hard or soft exudates may be present.

Moderate NPDR

- ❖ Microaneurysms and / or dot and blot hemorrhages in atleast one quadrant
- ❖ Soft exudates (Cotton wool spots)
- ❖ Venous beading or intraretinal microvascular abnormalities (IRMA)

Severe NPDR

When any one of the following 3 features is present

- ❖ Microaneurysms and intraretinal hemorrhages in all 4 quadrants
- ❖ Venous beading in 2 or more quadrants

- ❖ Moderate IRMA in at least 1 quadrant

  Known as the 4-2-1 rule

Very severe NPDR

When any two of the features of the 4-2-1 rule is present

II - Proliferative Diabetic Retinopathy

- ❖ Proliferation of new vessels, usually from the veins, is the characteristic feature
- ❖ New vessels on the optic disc (NVD)
- ❖ New vessels elsewhere on the retina, along the course of the retinal vessels (NVE)

III – Clinically significant Macular Edema (CSME)

- ❖ Presents with dimness of vision
- ❖ Retinal edema close to fovea
- ❖ Hard exudates close to fovea

Modified Klein Classification of diabetic retinopathy

ble 1. Modified Klein Classification of Diabetic Retinopathy

LEVEL	DEFINITION
1.0	No retinopathy
2.0	Microaneurysms (1 or more) only
3.0	Microaneurysms and 1 or more of the following: ·Retinal hemorrhage < standard photo #2A ·Hard Exudates (HE) < standard photo #3 ·Retinal infarcts questionably present ·Intraretinal microvascular abnormalities (IRMA) questionably present ·Venous beading (VB) questionably present ·Small venous loops definitely present
4.0	Microaneurysms and 1 or more of the following: ·Retinal hemorrhage > standard photo #2A ·HE > standard photo #3 ·Retinal infarcts definitely present ·IRMA definitely present ·VB definitely present
5.0	In fields 4 through 7 only: At least 3 of the following: ·Microaneurysms/retinal hemorrhage >= standard photo #2A in 1 field or more ·Retinal infarcts in at least 2 fields ·IRMA definitely present in at least 2 fields ·VB definitely present in at least 2 fields Or ·IRMA present in 4 fields and >= standard photo #8A in at least 2 fields
6.0	·New vessels on or within 1 disc diameter (DD) < standard photo #10A Or ·New vessels elsewhere or preretinal or vitreous hemorrhage, but level 7 definition not met
7.0	Diabetic Retinopathy Study (DRS) high-risk characteristics include one or more of the following: · New vessels elsewhere > 1/2 disc area in any single photographic field when associated with fresh vitreous or preretinal hemorrhage in any field · New vessels on or within 1 DD of the disc graded < standard photo #10A with preretinal or vitreous hemorrhage · New vessels on or within 1 DD of disc graded >= standard photo #10A with or without preretinal or vitreous hemorrhage
8.0	Unclassifiable due to large vitreous hemorrhage, Phthisis or enucleation secondary to Diabetic Retinopathy

Pathology and Implications of the features of DR

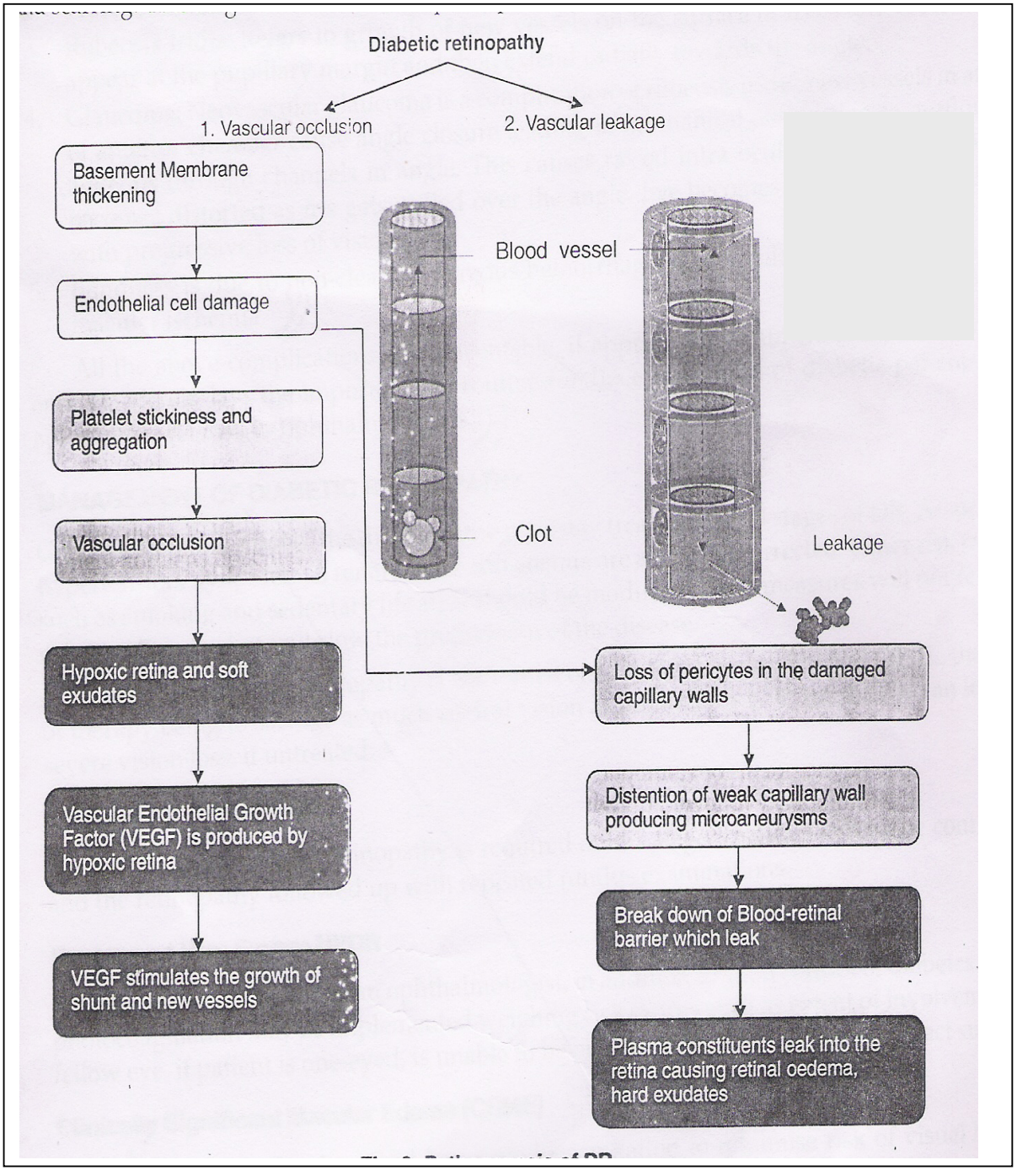
Diabetic retinopathy is caused by damage to blood vessels of the retina. Microaneurysm with microvascular leakage and occlusion are its hallmarks. Larger vessels may also be involved.

Saccular outpouchings of the weakened, damaged capillary walls produces microaneurysms. In the earlier and less severe stages of NPDR, these damaged blood vessels become porous and leak fluid into the retina. This breakdown of blood retinal barrier results in retinal oedema and hard exudates. Oedema occurring at the macula (CSME) causes blurred vision and requires immediate treatment as it can lead to serious loss of vision.

Extensive microaneurysm, hemorrhages in all parts of the retina and venous beading occurring in the later stages of NPDR (Severe to very severe NPDR) implies imminent neovascularisation (growth of new vessels). Hence early detection of this stage is crucial.

Various diabetes induced pathologic changes of the capillary walls and the blood cells results in microvascular occlusion leading to hypoxia of the retina. The hypoxic retina, probably attempting to

reestablish circulation, releases large amounts of vascular endothelial growth factor (VEGF), VEGF is a potent stimulator of angiogenesis, the growth of new blood vessels from pre-existing ones.[32]



These new vessels are fragile and can bleed causing loss of vision and scarring. This stage is liable to develop complications and therefore requires treatment.

SIGNS AND SYMPTOMS OF DIABETIC RETINOPATHY

SYMPTOMS :

1. Difficulty in reading
2. Blurring of vision
3. Sudden loss of vision in one eye
4. Seeing ring around lights
5. Dark spots or flashing light

SIGNS :

Diabetic retinopathy often doesn't have any symptoms or warning signs early on. At times the persons may suffer from macular edema which causes the vision to rapidly detoriate in a short period of time. Other experience problems with blurred vision where they see hollow around the centre of the objects.

The patient typically notice that they have problem with reading print even with the eye glass. Many patients notice their

visions weaken at night while others claims they have problem at day especially in bright sun light.

Complications of diabetic retinopathy

All are essentially complications of neovascularisation

1. Vitreous hemorrhage : Patient presents with sudden loss of vision, usually precipitated by straining while lifting a heavy weight or at the toilet and often is the presenting feature of undetected PDR.
2. Tractional retinal detachment (TRD)
3. Rubeosis Iridis : Refers to growth of new vessels on the surface of iris. New vessels first appear at the pupillary margin and then extend radially towards the angle.
4. Glaucoma : Neovascular glaucoma is a complication of rubeosis iridis, new vessels in angle of anterior chamber cause angle closure leading to mechanical obstruction to outflow of aqueous through channels in angle. This causes raised intra ocular pressure and becomes distorted as iris gets pulled over the angle. Eye becomes painful and red along with progressive loss of vision.

5. Blindness is due to non clearing vitreous hemorrhage, neovascular glaucoma, TRD and macular ischemia. [32]

All the above complications are preventable if appropriate treatment is instituted early enough. Herein lays the importance of routine fundus examination of diabetic patient and appropriate referral to ophthalmologists.

Screening for Diabetic retinopathy

The methods of screening for diabetic retinopathy includes

1. Direct ophthalmoscopy
2. Indirect ophthalmoscopy
3. Stereoscopic colour film, fundus photography
4. Mydriatic or non mydriatic digital color photography
5. Monochromatic photography
6. Fluorescent angiography of fundus

Traditionally ophthalmogist have screened for diabetic retinopathy by dilating the pupil and performing indirect ophthalmoscopy in which entire retina is examined.

The **Gold standard** for the detection of Diabetic retinopathy consists of 30 degree, Streoscopic photography of seven standard fields on colour film as developed for the ETDRS, classification of diabetic retinonapthy.

Although retinal imaging program are important in improving access to care and identifying patients who need further evaluation they do not replace comprehensive eye examinations by an ophthalmologist.

Studies and articles related to Diabetes and Anemia

1. Prevalence and characteristic of Anemia in Diabetes [22]

Practical Diabetes, International Journal, Apr : 2008, Article : vol 25.

Adetunji, FWACP, A Olujohungbe, MRCP J. Ronand

This article states that there are an increasing number of patients with diabetes who have been found to be anemic without underlying evidence of chronic renal disease. Over 500 diabetic patients were studied and concluded that anaemia was common in the study population. Screening routinely for anemia of Annual Diabetic follow up clinic may be cheap and effective way of identifying patient at risk of diabetic related complications especially microvascular complication.

2. Anemia in Diabetes : An emerging complication of micro vascular diseases. [23]

Gurret Diabetes Review S. Jan 2005, November

Merlin Thomas, Richard macsav, George Serums

According to this article : In diabetic patients, anemia is 2-3 times more prevalent than non diabetic, may be due to diabetic

nephropathy induced, reduced erythropoietin systemic inflammation, autonomic neuropathy and reduced red cell survival. Anemia may be a significant factor in determining the outcome of Diabetic microvascular complications like retinopathy.

3. Recognizing Anemia in people with Diabetes [25]

National Anemia Action Council,
NAAC Article Published, March 11, 2009.

In this article, they state that anemia is a common concern and can occur in up to 25% of people with diabetes. This is because having diabetes for a long time can affect kidneys and nerves.

Dr. Janet McGill, diabetologist and associate professor of medicine at Washington University in St. Louis stated that “Anemia is an under recognized and under treated condition among diabetes that can seriously affect their health and well being.

Studies show that having anemia along with diabetes may increase the likelihood of developing diabetic eye disease, developing heart disease or having a stroke. People who have both diabetes and anemia are more likely to die earlier than those who have diabetes but not anemia. Fortunately, anemia can be treated

and benefits such as increased energy, activity level and improved quality of life can be achieved.

4. Unrecognised Anemia in patients with Diabetes, A cross sectional survey. [26]

Diabetic Journal .org content 26/4116

Merlin C, Thomas, MBCHB, Richard J, Macisaac, PhD, Con Tsalamandris, MBBS, David Power, MD., PhD and George Jerums, MD.

Prediction of proliferative Diabetic retinopathy with hemoglobin level. Archives of ophthalmology November 1, 2009 127 : 1494-1499.

According to this article anemia is common in diabetes, potentially contributing to the pathogenesis of diabetes complications. This study established the prevalence and independent predictors of anemia in a cross sectional survey of 820 patients with diabetes in long term follow up in a single clinic.

A full blood count was obtained in addition to routine blood and urine test results for all patients over a 2 year period to

encompass all patterns of review. Predictors of the most recent Hb concentration and anemia were identified using multiple and logistic regression analysis.

A total of 190 patients (23%) had recognized anemia (Hb <12 g/dl for women and <13g/dl for men). This prevalence is two to three times higher than for patients with comparable renal impairment and iron stores in the general population.

Anemia is a common accompaniment to diabetes, particularly in those with albuminuria or reduced renal function. Additional factors present in diabetes may contribute to the development of increased risk for anemia in patients with diabetes.

5. Erythropoietic stress and anemia in diabetes mellitus [27]

Pub Med, U.S. National Library of Medicine, National Institutes of Health. Nat Rev Endocrinol, 2009 Apr. 5 (4) : 204-10.

Singh DK, Winoocur P, FarringtonK. Lister Hospital, Coreys Mill Lane, stevenage, Hertfordshire, UK, dsingh4@nts.net.

Anemia is one of the world's most common preventable conditions, yet it is often overlooked, especially in people with diabetes mellitus. Diabetes related chronic hyperglycemia can lead

to a hypoxic environment in the renal intersititium, which results in impaired production of erythropoietin by the peritubular fibroblasts and subsequent anemia. Anemia in patients with diabetes mellitus might contribute to the pathogenesis and progression of cardiovascular disease and aggravate diabetic nephropathy and retinopathy. Anemia occurs earlier in patients with diabetic renal disease than in nondiabetic individuals with chronic kidney disease.

However, an emphasis on regular screening for anemia, alongside that for other diabetes related complications, might help to delay the progression of vascular complications in these patients.

6. Anemia and Diabetic Retinopathy in type II diabetes mellitus. [30]

JAPI 2010, February

Padmaja kumari Rani, Rajiv Raman, Sudhir R Rachepalli, Swakshyar Saumya Pal, Vaitheeswaran kulothungan, Praveena Lakshmipathy, Uthra Satagopan, Govindasamy kumaramanickavel, Tarun sharma.

This study conducted at Chennai population by Sankara Nethralaya group. The diabetic retinopathy epidemiology and molecular genetic study. (SN-DREAMS)

They estimated the prevalence of anemia in persons with type 2 diabetes mellitus and its role as a risk factor for the presence and the severity of diabetic retinopathy, in a population based study.

5999 subjects from the general population aged >40 years were enumerated for the study. A total of 1414 persons identified with diabetes underwent comprehensive eye examination, and stereoscopic digital fundus photography was used for diabetic retinopathy grading. All patients underwent hemoglobin estimation for detection of anemia. Univariate and multivariate analyses were done to determine the independent risk factors for anemia.

The prevalence of anemia (Hb <12g/dl in women and <13g/dl in men) was 12.3%. Between 40 and 49 years of age, prevalence of anemia was higher in women than in men (26.4 % vs 10.3%). Men with anemia, and not women, had 2 times the risk of developing diabetic retinopathy.

Studies and articles related to Diabetic retinopathy and anemia

7. Diabetic Retinopathy : An Indian perspective. [19]

Indian Journal of Medicine 125, March 2007, page 297-310.

M. Ramar& R. Pradeepa

The above mentioned study states that Anemia is considered as a risk factor, for diabetic retinopathy because of reduced amount of oxygen for the retinal tissue.

The diabetic retinopathy in patients with low Hb levels have five fold increase risk of severe retinopathy compared to those with higher hemoglobin level.

8. Metabolic control and diabetic retinopathy [20]

Current diabetes revised 2009 page 5, 3, 7

Monikar Rodriguer – fontel, John B. Kernison, D. Vivsil Rifaro

This article states that ‘ the independence risk factor for progression to proliferative diabetic retinopathy are high levels of HbA1C, decreased hematocrit, decreased haemoglobin and increased serum lipids.

9. Seeing between the lines [21]

American diabetes Association

Clinical Diabetes 2003

IRL B Hirch. M.D.,

This study article shows that anemia appears to be an independent risk factor for diabetic retinopathy. Further more acute reduction in hematocrit may present in exacerbation of retinopathy. Retinal hypoxia is probably the most important mechanism.

10. Diabetic Retinopathy[8]

Study Report by D.Davis, MR Fisher, RE Gangnon, F. Barton, L.M. Aiello, E.Y. Chew, L. Ferris 3rd and GL. Knatterud

In their study, they showed that the risk factors for the development of high risk proliferative diabetic retinopathy (PDR) and for the development of severe visual loss were increased severity of non proliferative retinopathy, decreased visual acuity (or increased extent of macular edema), higher glycosylated hemoglobin, diabetic neuropathy, low hematocrit.

Studies and articles related to Pathogenesis of anemia and retinopathy

11. Anemia and elevated systemic levels of vascular endothelial growth factor (VEGF) [28]

Pub Med, U.S. National Library of Medicine, National Institutes of Health. Dunst J, Becker A, Lautenschager C, markau, S, Becker H, Fischer K, Haensgen G,

Department of Radiation oncology, Martin-Luther University Halle-Witenberg, Juergen, dunst @ medizin, unihalle, de

According to this article, Tissue hypoxia is a major stimulus for the upregulation of vascular endothelial growth factor. Anemia might impact on angiogenesis via impairment of tissue oxygenation.

The plasma VEGF levels were significantly elevated in patients with and without cancers (67.0 +/- 47.5 vs 88.9 +/- 68.8 pg/ml, n.s.). In a multivariate model, a significant association between low hb levels and increased plasma levels of VEGF was confirmed. In 16 patients with renal anemia, changes in plasma VEGF levels decreases after increase in Hb level (p=0.01).

Conclusion : Anemic patients have elevated levels of VEGF. The data suggest that anemia might impact on the progression of angiogenesis.

12. Association of the VEGF with proliferative Diabetic Retinopathy in Diabetes [29]

David Ray, Manoj Mishra, Shirley Ralph, Ian Read, Robert Davies and Paul Brenchley.

Dr. David Ray, University of Monchester, Endocrine science research groups.

Diabetic retinopathy and nephropathy cause significant morbidity in patients with diabetes. Vascular endothelial growth factor (VEGF) is a potent angiogenic and vascular permeability factor and is implicated in both of these diabetes complications. They reported in their study showing the VEGF -460 and VEGF +405 polymorphisms to increase basal VEGF promoter activity by 71% compared with the wild type sequence. And also showed the association of VEGF polymorphisms with proliferative diabetic retinopathy and diabetic nephropathy.

The VEGF – 460 genotype was predictive of retinopathy, even after controlling for blood pressure, glycemic control, duration of diabetes and obesity (p=0.02). The VCGF - 460C polymorphism is a positive independent predictive factor for the development of proliferative diabetic retinopathy.

13. Diabetic Retinopathy : An update [31]

Indian Journal of Ophthalmology, Review Article : year 2008, Volume 56, Issue : 3, page 179-188.

Ramandeep Singh, Kim Ramasamy, Chandran Abraham, Vishali Gupta, Amod Gupta, Department of ophthalmology, Postgraduate Institute of Medical Education and Research, Chandigarh, India, Apollo First Med Hospital, Chennai, Tamilnadu, India.

They state that currently there has been a great interest in vasoproliferative factors, which induce neovascularization. It has been shown that retinal ischemia stimulates a pathologic neovascularization mediated by angiogenic factors, such as vascular endothelial growth factor (VEGF), which results in proliferative

diabetic retinopathy (PDR), VEGFs are released by retinal pigment epithelium, pericytes and endothelial cells of the retina.

In ETDRS, low hematocrit levels at baseline were identified as independent risk factor for the development of high risk PDR and severe visual loss. It showed an increased risk of retinopathy in patients with the hemoglobin level of less than 12 g / dl. Anemia induced retinal hypoxia is speculated as cause of development of microaneurysms and other retinopathy changes.

Studies and articles regarding treatment of anemia and retinopathy

14. Spontaneous closure of micro aneurysm in Diabetic retinopathy with treatment of coexisting anemia. [18]

British Journal of ophthalmology, 2005,

R. Signhi, V. Gupta Dr. Gupta, A. Bhanusali.

In this article, they state that pathogenesis of diabetic retinopathy is multifactorial and various potential risk factors including HT, proteinuria, Duration of diabetes, chronic renal failure and anemia.

While Anemia has been found as an independent risk factor for development of high risk proliferative diabetic retinopathy. It has not received due attention in the management of diabetic retinopathy and they report a case of 34 year old man with diabetes with coexisting nutritional anaemia who showed spontaneous closure of the micro aneurysm after correction of the anemia and metabolic control.

15. Diabetic retinopathy [24]

Treating systemic condition aggressively can save sight

Clevel and Clinician , Journal of medicine : Nov 5, 2005

Stephen, H Sinchair, M.D., Cheive Delereci, Richard Macanut MD

According to this article, Anemia often accompanies, Diabetic kidney disease and is thought to exacerbate the ischemic aspect of diabetic retinopathy.

Studies of iron supplementation or erythropoietin treatment on retinopathy are few and they suggested treatment of anemia is associated with fewer new showers of retinal infarct, which may

result in a slow progression of capillary non perfusion and development of proliferative retinopathy.

AIM OF THE STUDY

1. To estimate the prevalence of anemia in patients with type 2 diabetic mellitus
2. And its role as a risk factor for the presence and the severity of diabetic retinopathy in Govt. Rajaji Hospital diabetic patients.

MATERIALS AND METHODS

- The study was conducted in both inpatients and out patients of Government Rajaji Hospital, Madurai.
- Most commonly in the outpatients of Diabetes department
- The study was conducted from October 2009 to September 2010.
- A total of 100 patients were taken for this study.
- Among the 100 patients, 50 were male and remaining were females.

DESIGN OF STUDY: Cross sectional analytic study

Selection Criteria :

Inclusion Criteria:

1) All the patients selected for the study were aged 40 years and above 40 years.
2) All the patients selected for the study had type 2 diabetes
3) All the patients selected for the study were attending Govt. Rajaji hospital in patient out patient department.

Exclusion Criteria :

1) Patients having type I diabetes were excluded from the study.
2) Patient with age below 40 years were excluded from the study.

Among the selected patients following variables were taken into the consideration.

1. Gender
2. Age
3. Haemoglobin
4. Blood pressure
5. Duration of the diabetes
6. Albuminuria
7. Diabetic retinopathy

Gender :

Among the 100 patients 50 were male and remaining were female.

Age : According to the age, patients were categorized

1. 40 – 49 years,
2. 50 – 59 years,
3. 60 – 69 years, and
4. Above 69 years.

Duration of Diabetes :

The duration of diabetes categorized as

1. < 5 years,
2. > 5 years

Blood pressure :

Systolic BP < 140, > 140 mmHg

Diastolic BP < 90, > 90 mm Hg

Albuminuria :

Patient has categorized as

Absent or Normo albuminuria

Micro albuminuria

Macro Albuminuria

Haemoglobin :

Categorized as

Anemia and

without anaemia

Retinopathy :

Presence or Absence of retinopathy

Definitions :

Anemia :

According to the WHO guidelines, Anemia was defined as haemoglobin concentration < 13 g / dl in men and < 12 g / dl in women

Hypertension :

Hypertension was defined as systolic BP > 140 mmHg, Diastolic BP > 90 mmHg or patient was on anti hypertensives medication.

Albuminuria :

Patient was considered as normo albuminuria or absent if albumin creatinine ratio was < 30 mg / g

Microalbumuneria :

If ACR between 30 – 300 mg / g

Macro albumuniria

If ACR was above 300 mg /g

Diabetic retinopthy :

Non sight threatening diabetic retinopathy includes

1. Mild nonproliferative diabetic retinopathy

2. Moderate non proliferative diabetic retinopathy

Sight threatening retinopathy :

1. Severe nonproliferative diabetic retinopathy
2. Proliferative diabetic retinopathy
3. Macular edema

Procedure done for the present study

Estimation of haemoglobin

Haemoglobin estimation was done by using capillary method by calory metric haemoglobunometer (Automated analyzer) in Govt. Rajaji Hospital.

Hb Estimation :

The above Hb estimation was done for all the patients taken for the study.

According to the above estimation of haemoglobin patient were categorized by haemoglobin level as follows.

< 11g/dl,

11-12g/dl,

12-13 g /dl

Abuminuria Estimation :

Albuminuria estimation was done by fully automatised iimuno turbidimetric assay method using the first morning sample of urine of the patient. The creatinine estimation was done by modified JAFFE method. By using this albumin, creatinine ratio was estimated. According to ACR, patient were categorized

Normo albuminuria or absent : ACR < 30 mg/g ,

Micro albuminuria : ACR 30 – 300 mg /g and

Macro albuminuria : ACR :above 300 mg/g.

Blood pressure :

Blood pressure of all the patients were recorded at rest, sitting posture in right upper limb with sphygmomanometer and categorized those with

SBP < 140 mmHg, > 140 mmHg,

DBP < 90 mm Hg, > 90 mm Hg

Fundus examination and diabetic retinopathy grading

All the patients were examined for the diabetic retinopathy after dilating the fundus at ophthalmology department by ophthalmologist in Government Rajaji hospital and the fundus

changes for the diabetic retinopathy by using modified Kelin classification were recorded as absent retinopathy, non proliferative retinopathy, proliferative retinopathy, macular edema. Further categorized to absent retinopathy and retinopathy present. Patients having retinopathy were further divided into non sight threatening retinopathy or sight threatening retinopathy.

RESULTS AND ANALYSIS

The study was conducted on 100 patients in the outpatients and inpatients attended Diabetology opd and GRH opd, Madurai.

The estimation of haemoglobin and presence of and absence of albuminuria was done. The measurement of the blood pressure of the patient was done. The results were analysed effect of anemia on diabetic retinopathy as well as severity of retinopathy. And aslo comparing anemia with age, gender, alminuria and blood pressure diabetic retinopathy.

The females and males analyzed separately on age, hypertension, Albuminuria, retinopathy and severity of retinopathy. The gender influence of anemia and retinopathy was analyzed.

Age vs Anemia in females Table -1

In our study, we taken 50 females diabetes out of which 40 patients had anemia. (80%) remaining 20% have no anemia.

Among the anemic group anemia is present 92.2% in 40-49 years age group that is in younger age group and 83.3% in 50-59 years .

We also observe anemia was comparatively less in older age (60-69 years and above 69 years.).

Table – 1

AGE VS ANEMIA (n=50)

FEMALE (Yrs)	ANAEMIA				
	POSITIVE		NEGATIVE		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
40-49	20	95.2%	1	4.8%	21
50-59	10	83.3%	2	16.7%	12
60-69	05	55.6%	4	44.4%	09
70+	05	62.5%	3	37.5%	08
TOTAL	40		10		50

The above tables shows that anemia present in 40-49 age group is 95% followed by 83.3% in 50-59 years age group.

Table - 2

ANAEMIA Vs RETINOPATHY (n=50)

FEMALE (Hb in grams%)	RETINOPATHY				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<12%	26	65.5%	14	35%	40
>12%	10	100%	00	0.00%	10
TOTAL	36		14		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		4.861a	1	0.027	

The above table shows that retinopathy is present in 35% of the cases in anemia group (hb < 12%) when comparing to non anemia group (hb >12 %) is 0 %. P value is 0.027.

Anemia Vs Retinopathy :

In 50 cases of females with diabetic anemia was present in 40 cases Anemia was not present in 10 cases. Among the anemia group the retinopathy was present 35% comparing with non anemic group it was 0%. The Chi square test showed p value of 0.027. So in female with anemia presence of retinopathy was statistically significant.

Table - 3

ANAEMIA Vs ALBUMINURIA(n=50)

FEMALE (Hb in grams%)	ALBUMINIURIA				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<12%	27	67.5%	13	32.5%	40
>12%	10	100%	00	0.00%	10
TOTAL	37		13		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		4.392a	1	0.036	

Table 3

Among the 50 female diabetics Albuminuria were present in 13 case of anemia group whereas albuminuria absent in non anemic patient. The chi square test showed the p value of 0.036. So in female diabetic presense of anemia statistically significant for the albuminuria.

The above table shows that albuminuria is present in 32.5% of the cases in anemia group (hb < 12%) when comparing to non anemia group (hb >12 %) is 0 %. P value is 0.036.

Table - 4

ANAEMIA Vs HYPERTENSION(n=50)

FEMALE (Hb in grams%)	HYPERTENSION				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<12%	26	65.0%	14	35.0%	40
>12%	10	100%	00	0.00%	10
TOTAL	36		14		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		4.861a	1	0.027	

Table 4

In female diabetics hypertension was present in 33% in anemia patients whereas non anemic group it was only 0%. The chi square test showed the p value of 0.027. So in female presense of anemia is statistically significant for the hypertension.

The above table shows that hypertension is present in 35% of the cases in anemia group (hb < 12%) when comparing to non anemia group (hb >12 %) is 0 %. P value is 0.027.

Table – 5 Duration Vs Retinopathy

FEMALE (Duration DM YRS)	RETINOPATHY				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<5%	24	100%	00	0.00%	24
>5%	12	46.2%	14	53.8%	26
TOTAL	36		14		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		17.949a	1	0.000	

In female diabetics duration of diabetes more than 5 years group the retinopathy was 53.8% was compared to duration of less than 5 years was only 0%. The chi square test showed the p value of 0.000. So in female duration more than 5 years is statistically significant for retinopaty.

Table – 6

DURATION VS ALBUMINURIA

FEMALE (Duration DM YRS)	ALBUMINURIA				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<5%	23	95.8%	01	4.2%	24
>5%	14	53.8%	12	46.2%	26
TOTAL	37		13		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		11.435a	1	0.001	

The above table shows that albuminuria is present in 46.2% in diabetes mellitus duration of more than 5 years as comparing to diabetes less than 5 years group is 0%. P value is 0.001.

Table – 7AGE VS ANEMIA (n=50)

MALE (Yrs)	ANAEMIA				
	POSITIVE		NEGATIVE		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
40-49	01	6.70%	14	93.3%	15
50-59	03	23.1%	10	76.9%	13
60-69	10	62.5%	06	37.5%	16
70+	06	100%	00	0.00%	06
TOTAL	20		30		50

The above tables shows that anemia present in more than 70 age group is 100% followed by 62.5% in 60-69 years age group. Anemia is less in younger age group ie. 6.7%.

Table 7

In male patient age vs anemia showed anemia was present in older age than younger age in contrary to female diabetes. In young age of 40-49 years it was only 6.7% and 50-59 years it was 23.1% while in the older age 60-69 years. It was 62.5% the above 70 it was 100%.

Table – 8

ANEMIA VS RETINOPATHY (n=50)

MALE (Hb in grams%)	RETINOPATHY				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<13%	00	0.00%	20	100%	20
>13%	30	100%	00	0.00%	30
TOTAL	30		20		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		50.000a	1	0.000	

Table 8

In male patient with anemia the percentage of retinopathy was 100% as compared to non anemic group it was 0%. The chi square test showed the p value of 0.000. So in male presence of anemia is statistically significant for the diabetic retinopathy.

The above table shows that retinopathy is present in 100% of the cases in anemia group (hb < 13%) when comparing to non anemia group (hb >13 %) is 0 %. P value is 0.000.

Table – 9

ANEMIA VS ALBUMINURIA (n=50)

MALE (Hb in grams%)	ALBUMINIURIA				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<13%	8	40	12	60	20
>13%	30	100	0	0	30
TOTAL	38		12		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		23.684a	1	0.000	

Table 9

In 50 male diabetic patient with anemia albuminuria was present in 60% as compared to non anemic group it was 0%. The chi square test showed the p value of 0.000. So in male diabetes with anemia is statistically significant for the albuminuria.

The above table shows that albuminuria is present in 60% of the cases in anemia group (hb < 13%) when comparing to non anemia group (hb >13 %) is 0 %. P value is 0.000.

Table -10

ANEMIA VS HYPERTENSION

MALE (Hb in grams%)	HYPERTENSION				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<13%	09	45.0%	11	55.0%	20
>13%	30	100%	00	0.00%	30
TOTAL	39		11		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		21.154a	1	0.000	

Table 10

In males hypertension was present in 55% of patient with anemia the non anemic group it was 0%. The chi square test showed the p value of 0.000. So in male presence of anemia is statistically significant for the iabetic retinopathy.

The above table shows that hypertension is present in 55% of the cases in anemia group (hb < 13%) when comparing to non anemia group (hb >13 %) is 0 %. P value is 0.000.

Table – 11

DURATION VS RETINOPATHY

MALE (Duration DM YRS)	RETINOPATHY				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<5%	20	100%	00	0.00%	20
>5%	10	33.3%	20	66.7%	30
TOTAL	30		20		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		22.222a	1	0.000	

The above table shows that retinopathy is present in 66.7% in diabetes mellitus duration of more than 5 years as comparing to diabetes less than 5 years group is 0%. P value is 0.000.

Table 11

In males patients with diabetic more than 5 years, retinopahty was present in 66.7 % whereas < 5 years it was 0%. The chi square test showed the p value of 0.000. So in male duration of diabetes more than 5 years statistically significant for the diabetic retinopathy.

Table 12.

DURATION Vs ALBUMINURIA (n=50)

MALE (Duration DM YRS)	ALBUMINURIA				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<5%	20	100%	00	0.00%	20
>5%	18	60.0%	12	40.0%	30
TOTAL	38		12		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		10.526a	1	0.001	

The above table shows that albuminuria is present in 40% in diabetes mellitus duration of more than 5 years as comparing to diabetes less than 5 years group is 0%. P value is 0.001.

Table 13

Comparing the gender influence on retinopathy the male with anemia retinopathy was 100%. In female it was 35% in anemia group. The chi square test showed the p value of 0.000. So influence and retinopathy is statistically significant for the diabetic retinopathy. It is anemia which is influence on the retinopathy not gender.

Table 13.
ANAEMIA Vs RETINOPATHY

GENDER INFLUENCE

GENDER				
	ANAEMIA		RETINOPATHY	
	No.of cases	PERCENT	**No.of cases**	PERCENT
MALE(50)	20	40%	20	100%
FEMALE(50)	40	80%	14	35.0%

CHI SQUARE TESTS			
	Value	df	P value
Pearson chi-square	98.28a	1	0.000

The above table shows that the retinopathy present in males with anemia group is 100% as comparing to female anemic group retinopathy present is only 35%.

Table 14.ANAEMIA Vs SEVERE RETINOPATHY(n=50)

FEMALE (Hb in grams%)	SIGHT THREATENING RETINOPATHY				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<12%	37	92.5%	03	7.5%	40
>12%	10	100%	00	0.00%	10
TOTAL	47		03		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		0.798a	1	0.372	

Table 15.ANAEMIA Vs SEVERE RETINOPATHY(n=50)

MALE (Hb in grams%)	SIGHT THREATENING RETINOPATHY				
	ABSENT		PRESENT		TOTAL
	No.of cases	PERCENT	**No.of cases**	PERCENT	
<13%	15	75%	05	25%	20
>13%	30	100%	00	0.00%	30
TOTAL	45		05		50
CHI SQUARE TESTS					
		Value	df	P value	
Pearson chi-square		8.333a	1	0.004	

Table 14

In female patient with anemia the severe form of sight threatening retinopathy was 7.5 % comparing to non anemia group the percentage is 0%. p value is 0.372. Statistically not significant So in female the presence of anemia is not a risk factor for the severe retinopathy. But the number of patient with severe retinopathy was less comparing to non severe group.

Table 15

In male patient with anemia the severe form of sight threatening retinopathy was present 25 %. Comparing non anemic group 0 % with p value .004. So in male presence of anemia is statistically significant for the severity of retinopathy. So in male presence of anemia is a risk factor for the severity of retinopathy.

DISCUSSION

In our study we analysed the significance of anemia in type 2 diabetic patients with retinopathy and compared anemia with other risk factors like gender,albuminuria,duration of diabetes and hypertension both in males and females separately

In our study results we observed that the percentage of anemia in type 2 diabetes was more than we expected.

The anemia is more common in diabetic both men and women.In our study we also observed that the percentage of anemia in women with type2 diabetes is more than men.

The study also shows that anemia is more in younger women than in men.In females aged 40-49 yrs maximum percentage of anemia was noted (95.2%)and in men it was at its maximum between 60-69 yrs (62.5%)and above 70 yrs(100%).

After the fifth decade however there was no difference in the anemia noted both in women and men .The possible reasons would be the onset of menopausal period around this age in women as the literature shows.

In our study we observed that the diabetic patient with anemia are more likely to develop diabetic retinopathy than without anemia. In men

the risk of developing diabetic retinopathy is increased as compared with women. This observation is supported by the study by Quing Quiou et al[6] They reported the odds ratio of 2 for the presence of diabetic retinopathy and retinopathy increased with anemia, in a cross sectional study of more than 1600 individuals with type 2 diabetes mellitus.

In our study we observed females with anemia the percentage of diabetic retinopathy was 35% compared with females without anemia 0%.

We also observed men with anemia, the diabetic retinopathy was 100% compared with the men without anemia (0%). (100% Vs 0%) with significant P value (0.000).

In our study we found that sever sight threatening Retinopathy was present in 5 cases in men. The statistical analysis of anemia versus sever Retinopathy showed. Significant P value (0.002) so in men anemia is a Risk factor for the severity of retinopathy.

In our study we also found that sever sight threatening retinopathy was present in 3 cases in women. The statistical analysis of anemia versus sever Retinopathy showed no Significant P value (0.002) so in women anemia is not a Risk factor for the severity of retinopathy.

These observation is supported by the study done by Dr.Gupta et.al., they reported anemia was an Independent risk factor for High risk sever Prolifirative Retinopathy.

This observation is also supported by the study by Davis et al ETDRS[8] (Early treatment diabetic retinopathy study) evaluated the effect of anemia on retinopathy by hematocrit measurement. They reported that in low hemotocrit group (< 40 % in month and < 35% in females) retinopathy was noted and reported anemia as an independent risk factor for the development of high risk. Diabetic retinopathy and serve vision loss over a 5 year follow with odds ratio of 1.52.

Similar risk of anemia with sever retinopathy was also recorded in case series by Shorb et al [9].

Other observation of our study shows, albuminuria is present in 60% of men with anemia and it is 0% men without anemia on the other hand the observation shows albuminuria is present in 32.5% in women with anemia and 0% in Non anemic group. Eventhough the effect of anemia an albuminuria is statistically significant P value is observation is probably not entirely due to anemia. Presence of anemia increases the likehood of albuminuria.

In our study we found that in men with anemia the hypertension is present in 55% comparing to non anemic group 0% is observed. Also true for female with anemia with significant P value. Eventhough our study showed the significances of anemia on hypertension it is not entirely due to anemia because Hypertension is Multi factorial cassation. Presence of anemia increases the likehood of hypertension.

In our study, we observed the duration of diabetes is definitely influencing with retinopathy and albuminuria (66.7% vs 0, 40 Vs 0, 53 vs 0, 46.2 vs 0) in men and women respectively.

Finally, detection of anemia and its treatment is important in the management of diabetic retinopathy. In those patients who had both anemia and diabetic mellitus Friedman and associates[14] reported that the treatment of anemia with erythropoietin was correlated with substantial resolution of macular hard exuadate. The improved haemoglobin concentration with therapy of anemia improves the tissue oxygenation and may result in reduced VEGF production which improves this hyperpermeability and reduces the stimulous for neovascularization. There by prevents the new vessel formation in retina and reduce the diabetic retinopathy. So these observations suggest that anemia evaluation should be considered in routine management of persons with

diabetic and could be treated to minimize the risk of micro vascular complications like retinopathy.

Eventhough our study and previously done other studies like SN DREAMS, Padmaja kumar et al[10] also showed the anemia in type 2 diabetic patient is a risk factor for the presence of diabetic retinopathy the cause and relationship between anemia and diabetic retinopathy has to be proved by longitudinal studies in near future.

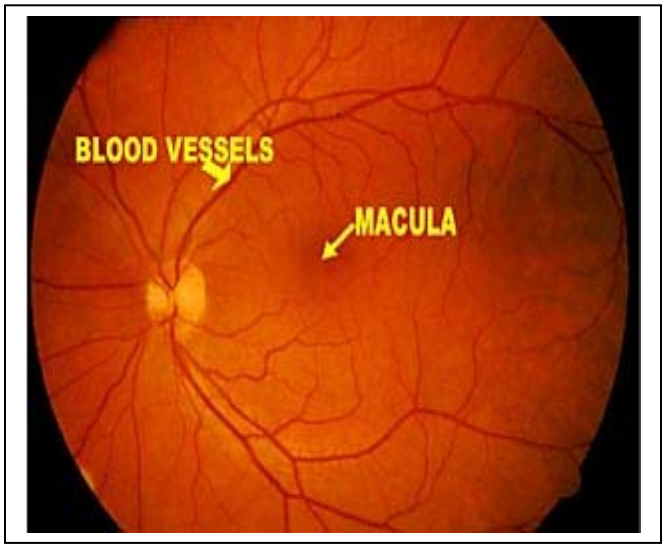
SUMMARY

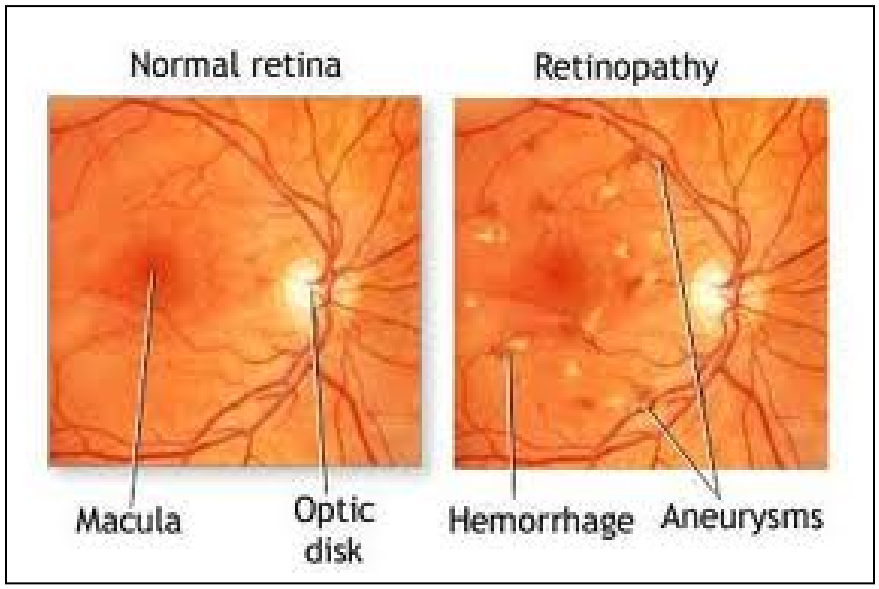
1. As every body know, the incidence of type 2 diabetes mellitus is increasing world wide especially in India. Among the complications of diabetes mellitus, retinopathy is the most important, dreadful and devastating complication as loss of vision is inevitable without treatment.
2. Anemia is more common in diabetic population. And anemia in diabetic women is more common than men and also more common in young women than young men.
3. The presence of anemia in type 2 diabetes mellitus patients is a risk factor for the development of diabetic retinopathy.
4. Infact, anemia is an independent risk factor for the presence of diabetic retinopathy.
5. The percentage of retinopathy in men is more than women in anemic group. Severity of retinopathy is more in men with anemia.
6. So, early detection of anemia and treating it will save the sight of Millions and Millions of people with diabetes.

CONCLUSION

1. Diabetes mellitus is one of the serious disease affecting the largest population world wide.
2. Diabetic retinopathy is a sight threatening preventable complication.
3. Anemia is more common in Diabetic population both men and women.
4. Anemia is one of the independent risk factor for the presence of diabetic retinopathy.
5. Presence of anemia in men is risk factor for severe form of diabetic retinopathy.
6. Along with life style modification and strict glycemic control, early detection of anemia in diabetic patient and treating the anemia irrespective of the cause of anemia will prevent the micro vascular complications especially diabetic retinopathy.
7. Every tenth individual in diabetic population could be anemic.
8. Identifying and treating anemia would make a great impact in managing diabetic retinopathy.

NORMAL FUNDUS





DIABETIC RETINOPATHY

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